

# Schnitzler Syndrome: Beyond the Case Reports: Review and Follow-Up of 94 Patients with an Emphasis on Prognosis and Treatment

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**Objective:** Schnitzler syndrome is a rare disorder characterized by a chronic urticarial rash and monoclonal gammopathy, accompanied by intermittent fever, arthralgia or arthritis, bone pain, and lymphadenopathy. To systematically review disease characteristics of Schnitzler syndrome and collect follow-up information to gain insight into treatment efficacy and long-term prognosis.

**Methods:** PubMed and MEDLINE databases (1966-2006) were searched, using the key words “Schnitzler syndrome,” and the combination of “urticaria” with “monoclonal gammopathy,” “immunoglobulin M (IgM),” or “paraproteinemia,” as well as secondary references. Data on a total of 94 patients who met the criteria for Schnitzler syndrome were reviewed. Questionnaires sent to all authors retrieved additional follow-up data on 43 patients, resulting in a mean follow-up of 9.5 years after onset of symptoms, and a follow-up of 20 years or more in 10 patients.

**Results:** Symptoms, signs, and laboratory findings as found in the 94 patients are reviewed in detail. There have been promising developments in therapeutic options, especially antiinterleukin-1 treatment, which induced complete remission in all 8 patients treated so far. To date, no spontaneous complete remissions have been reported. Patients with Schnitzler syndrome showed no increased mortality during the present follow-up. However, they had a 10-year risk of 15% of developing a lymphoproliferative disorder, most notably Waldenström’s macroglobulinemia. Three cases of type amyloid A (AA) amyloidosis associated with Schnitzler syndrome were reported.

**Conclusions:** Schnitzler syndrome is a disabling disorder which affects multiple systems and which can be considered as an autoinflammatory syndrome. There are new, effective treatment options, but close monitoring remains warranted because of the increased risk of lymphoproliferative disease.

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**Keywords:** *Schnitzler syndrome, urticaria, monoclonal gammopathy, autoinflammatory, Waldenström’s macroglobulinemia, anakinra*

Schnitzler syndrome is a rare disabling disorder characterized by a chronic urticarial rash and a monoclonal immunoglobulin M (IgM) gammopathy, accompanied to varying degrees by intermittent un-

explained fever, arthralgia or arthritis, bone pain, lymphadenopathy, hepato- or splenomegaly, leukocytosis, and an elevated erythrocyte sedimentation rate (ESR) (1). Because patients often present to various specialists with different symptoms, and because the disorder is little known, it can take years before the correct diagnosis is made.

In 1972, the French dermatologist, L. Schnitzler, was the first to describe this constellation of symptoms and signs (2), and to date, 89 cases have been reported. However, these are mostly confined to case reports, written at the time of diagnosis of the patient, and yield relatively little information on long-term disease progression and

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H.D.K. is supported by a grant from Studiefonds Ketel 1; A.S. is supported by a ZonMW Veni grant.

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prognosis. We reviewed all 89 reported cases and 5 previously unpublished cases with Schnitzler syndrome and obtained follow-up data by contacting authors (1-72) (Nikolova, Akhras, Lachmann, Gül, and Brinkman, personal communication). Our main focus was treatment efficacy, course of disease, and prognosis.

## DEFINITION

Lipsker and coworkers introduced a set of diagnostic criteria for Schnitzler syndrome (1). They proposed that a diagnosis of Schnitzler syndrome could be made in a patient with a combination of an urticarial skin rash, a monoclonal IgM component, and at least 2 of the following criteria: (recurrent) fever, arthralgia or arthritis, bone pain, lymphadenopathy, hepato- or splenomegaly, leukocytosis, an elevated ESR, and abnormal findings on bone morphologic investigations (Table 1) (1). Importantly, other causes must have been excluded (see “Differential diagnosis”). In recent years, a variant Schnitzler syndrome has been defined, characterized by an IgG monoclonal gammopathy instead of IgM (3,6,19,29,49,53,60) (Gül, personal communication). We follow these criteria in the present review.

## METHODS

We performed a literature search of Medline and PubMed (1966-2006), using the key words “Schnitzler syndrome,” and the combination of “urticaria” with “monoclonal gammopathy,” “IgM,” or “paraproteinemia.” References revealed many additional articles mostly in the English and French literature. Personal communication yielded 4 additional unpublished cases, from Bulgaria, the United Kingdom, Turkey, and the Netherlands (Nikolova, Akhras, Lachmann, Gül, and Brinkman, personal communication). We set up a database with patients’ characteristics, signs and symptoms, treatment effects, and course of disease, in which we included all patients who

Table 1 Diagnostic Criteria for SS

Major: (Chronic) urticarial rash Monoclonal IgM (or IgG: variant type)
Minor: Intermittent fever Arthralgia or arthritis Bone pain Lymphadenopathy Hepato- and/or splenomegaly Elevated ESR and/or leukocytosis Bone abnormalities (on radiological or histological investigation)

A patient can be diagnosed with Schnitzler syndrome when there is a combination of both major criteria and 2 or more minor criteria, after exclusion of other causes (see Differential diagnosis).

Adapted from Lipsker et al (1).

Table 2 Epidemiology: Country of Origin of Reported Patients

Country of Origin	Number of Patients
France	38
Germany	12
Spain	7
Italy	8
The Netherlands	6
United Kingdom	4
United States	4
Japan	3
Canada	2
Bulgaria	2
Others	8
Total	94

met the above-mentioned definition of Schnitzler syndrome. Patients with other diseases that might explain the findings were excluded. This database contains data on 94 patients at present. We sent questionnaires to the authors to collect more follow-up data, which we obtained on 43 patients. The mean duration of follow-up from start of symptoms in the 94 patients is 9.5 years. In 5 patients follow-up was less than 1 year, and in 10 of 94 patients it was 20 years or more. Survival analysis was performed using the Kaplan–Meier method, by GraphPad Prism version 4.02 for Windows (GraphPad Software, San Diego, CA, [www.graphpad.com](http://www.graphpad.com)).

## EPIDEMIOLOGY

During the 1970s to early 1990s, Schnitzler syndrome was reported solely in western European countries, especially in France. The majority of reported cases is still of French origin (Table 2). Presumably this is due to the fact that the disorder was originally published in French by a French physician (2). In the last decade, however, cases have been reported in countries all over the world, ranging from Australia (67) to the Czech Republic (50). As shown in Table 2, the vast majority of reported patients are western Europeans of white descent, but 3 Japanese cases are known as well (3,48,66). The reason for the relatively low number of patients reported from the US is unknown. Schnitzler syndrome is highly likely to be underdiagnosed.

Of the 94 cases, 57 are male (male:female ratio, 1.6). The mean age of onset is 51 years (SD, 12 years). The youngest patient reported had the first attack of urticaria at the age of 13 years (34). However, she is an exception, as symptoms started before the age of 35 years in only 4 other patients (5,15,52) (Gül, personal communication). There is a significant delay in diagnosis, ranging from several months to 20 years. In most cases the diagnostic delay exceeds 5 years (1).

No risk factors have been identified to date nor are there indications that Schnitzler syndrome is a familial disorder. There is only 1 patient known to have a relative

Table 3 Prevalence of Clinical Findings in SS Patients

Characteristic	Number of Cases		Frequency (%)
	Present	Reported*	
Chronic urticaria	94	94	100
Pruritus	29	64	45
Periodic fever	73	83	88
Arthralgia/arthritis	58	71	82
Bone pain	50	69	72
Weight loss	16	25	64
Lymphadenopathy	30	68	44
Hepatomegaly	18	63	29
Splenomegaly	8	65	12
Angioedema	4	88	5

\*Number of cases in which this information was available.

with a monoclonal IgM, in this case a patient's father (Clauvel, personal communication).

### ETIOLOGY/PATHOPHYSIOLOGY

The etiology of Schnitzler syndrome remains unknown. Several hypotheses have been proposed, most of which suggest the involvement of autoreactive antibodies. Lipsker and coworkers showed monoclonal IgM deposits in the skin of patients along basement membranes or in capillary walls and suggested that the in situ IgM-mediated complement activation and subsequent tissue damage might cause the urticarial skin lesions (73). However, these IgM skin deposits were only detected in approximately 25% of patients with Schnitzler syndrome and were also found in patients with Waldenström's macroglobulinemia (WM) without urticaria, which strongly suggests that this phenomenon plays no major pathophysiological role. De Castro and coworkers found heterogeneous histopathological changes in a study of 15 cases, although most cases demonstrated neutrophilic urticaria (17). Sperr and coworkers reported the detection of IgG<sub>3</sub> autoantibodies directed against cellular proteins, and IgG<sub>2</sub> antibodies specific for the  $\alpha$ -chain of the IgE receptor (Fc $\epsilon$ RI) in 1 patient's serum. They suggested that preferential T-helper cell type 1 (Th1) autoimmune reactions played a pathophysiological role (65). In addition, Saurat and coworkers reported the detection of IgG autoantibodies directed against the cytokine interleukin (IL)-1 $\alpha$  (74). However, other groups could not confirm these findings in their patients (8,20,39,44,48,57,65) and these anti-IL-1 $\alpha$  antibodies are present in about 18% of the general population (74).

Considerations regarding potential pathophysiological mediators in Schnitzler syndrome include the role of several cytokines. For example, an elevated concentration of IL-6 was found in some patients (18,48). As a major modulator of the acute phase response, IL-6 could be involved in the systemic features, and it was suggested that its effects on B-cell differentiation could form the link to the monoclonal gammopathy (74). However, increased levels

of cytokines are not sufficient evidence for a causal relationship (75).

The recent success of treatment with the IL-1 $\beta$  inhibitor, Anakinra, which invariably leads to complete remission (see "Treatment") (19,45) (Akhras, personal communication), seems to indicate a role for IL-1 $\beta$  as an important mediator in the pathophysiology of Schnitzler syndrome. IL-1 $\beta$  can cause both systemic inflammation and inflammation of the skin and is also a potent stimulator of bone resorption (76). The exact involvement of IL-1 $\beta$ , initiating factors, and cause of Schnitzler syndrome remain to be identified.

### MEDICAL HISTORY AND PHYSICAL EXAMINATION

The main clinical findings and the frequencies that were reported in patients with Schnitzler syndrome are shown in Table 3.

#### Chronic Urticaria

The hallmark of Schnitzler syndrome is a chronic, recurrent urticarial rash, which is usually the first symptom to occur. Chronic urticaria is defined as episodes of urticarial outbreaks that persist between 4 and 36 hours and recur for a duration of at least 6 weeks (77,78). The frequency of urticarial eruptions differs greatly among patients. It ranges from daily to twice a year, but in most cases the rash is present continuously. Individual lesions last 12 to 36 hours and resolve completely without scarring, while new ones appear daily. The urticarial rash consists of annular erythematous and maculopapular lesions that are 0.5 to 3 cm in diameter and sometimes confluent.

In Schnitzler syndrome, pruritus is usually absent at the onset of disease, but lesions became pruritic in approximately 45% of patients after several years. Severe antihistamine-resistant pruritus has been reported in only a few cases (56,65). The rash affects primarily the trunk and the extremities, sparing the palms, the soles, and the head and neck areas (Fig. 1). Some patients report aggravating factors, such as alcohol, spicy food, and stress (1,19). One publication reported the onset of Schnitzler syndrome in



Figure 1 Urticarial rash on the lower arm of a Schnitzler syndrome patient.

a patient 3 months after a severe maxillary sinusitis complicated by mycotic sepsis, and the authors suggested that this might have been an immunological trigger (5). Angioedema occurred in 4 cases (15,60).

### Periodic Fever

Recurrent spiking fever is the second most common symptom, affecting 88% of patients. Like the urticarial eruptions, the frequency of febrile episodes differs greatly among patients, ranging from daily to twice a year. The episodes usually resolve within a few hours but can persist for up to 24 to 48 hours. Peaks over 40°C are common, although chills are rare. The fever and rash usually, but not always, appear simultaneously.

### Musculoskeletal Symptoms

About 80% of patients complain of relapsing arthralgias. Commonly, the large joints are affected, including the hips, knees, wrists, and ankles, although other joints may be involved as well. The aching joints often appear normal. Frank arthritis was reported in 3 patients, 1 of whom experienced a flare-up of Schnitzler syndrome with oligoarthritis after a 2-year remission on corticosteroids (29,55) (Gül, personal communication). Joint destruction or deformities have not been reported.

Bone pain has been reported in 72% of cases, typically in the tibia and ilium. Other bones were incidentally affected, including the femur, forearm, spine, and clavicle. Some patients report myalgias: these may be hard to differentiate from bone pain.

### Other Symptoms

Lymphadenopathy was found in 44% of patients, usually in the axillary and inguinal regions. The lymph nodes can be persistent, multiple, and up to 3 cm large, at times necessitating a biopsy to exclude lymphoma. Hepatomegaly is also a common feature, and splenomegaly was found in 12% of patients. Many patients suffer from malaise and fatigue and weight loss is common. Incidentally reported symptoms include chronic inflammatory demyelinating polyneuropathy (9), pseudoxanthoma elasticum (30,44,68), headache, depression, and vertigo (30). Peripheral neuropathy associated with anti-MAG (myelin-associated glycoprotein) serum activity was seen in 2 patients (39,59). Monoclonal IgM antibodies against MAG can cause a chronic demyelinating polyneuropathy in which deposits of IgM are found on skin-myelinated nerve fibers (79), but the relationship with the paraprotein in Schnitzler syndrome is unclear. One patient developed severe thrombophilia with antiphospholipid syndrome and hyperhomocysteinemia (24). Another patient reported hearing loss; intriguingly, this resolved completely on treatment with an IL-1 inhibitor (19).

Table 4 Prevalence of Laboratory and Imaging Findings in SS Patients

Characteristic	Number of Cases		Frequency (%)
	Present	Reported*	
Laboratory			
Monoclonal gammopathy	94	94	100
• IgM $\kappa$ (1 case: +IgA)	81	94	86
• IgM $\lambda$	5	94	5
• IgG $\kappa$	7	94	7
• IgG $\lambda$	1	94	1
Elevated ESR	81	84	96
Leukocytosis	48	70	69
Anemia	31	55	56
Bence-Jones proteinuria	10	35	29
Histology (skin biopsy)			
Vasculitis	22	87	25
Radiographic imaging			
Abnormal bone morphology	36	75	48

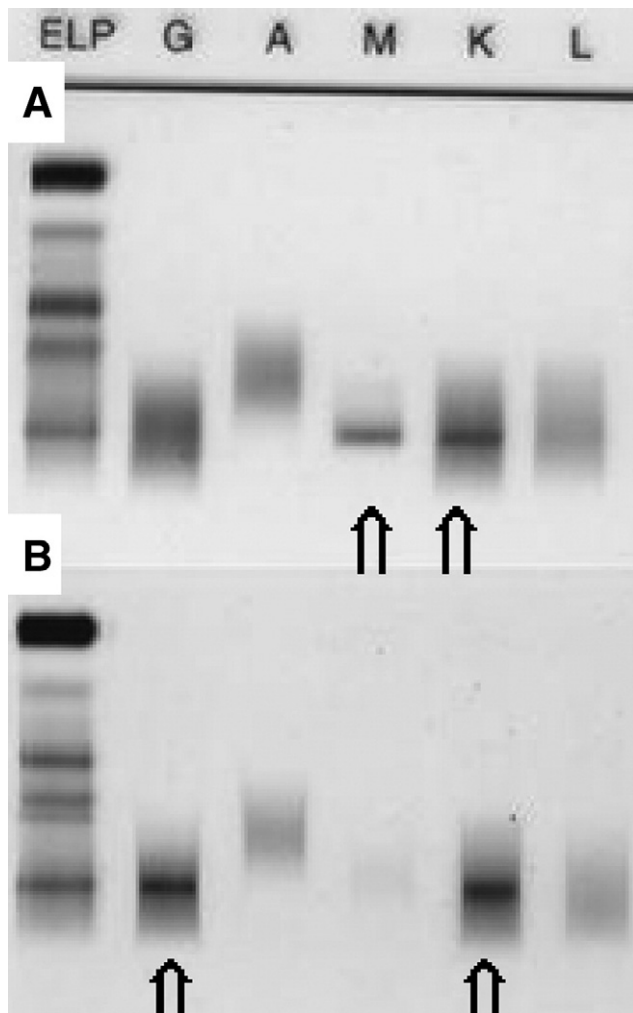
\*Number of cases from which this information was available.

### Laboratory, Histological, and Radiological Investigations

A monoclonal IgM component must be present to meet the diagnostic criteria. Alternatively, in the case of variant Schnitzler syndrome, it is a monoclonal IgG component (9% of the present cohort). However, at the time of presentation, the M-component may still be undetectable, only exceeding the threshold later in the course of disease. At the time of diagnosis, IgM concentrations do not exceed 10 g/L in more than two-thirds of cases.

In 94% of cases, light chains are of the  $\kappa$ -type (Table 4). Agarose gel electrophoresis followed by immunofixation is recommended for recognition of a paraprotein (80) (Fig. 2). IgM levels can either remain stable or show a progressive increase of about 0.5 to 1.0 g/L per year (1). A very high concentration of IgM may be an indication of WM. In 1 case, a monoclonal IgA gammopathy was reported in conjunction with a monoclonal IgM $\kappa$  gammopathy (44). Bence-Jones proteinuria was reported in 29% (10 of 35) of patients. IgA and IgG levels are decreased in approximately 25% of patients.

Signs of systemic inflammation will also be found: elevated ESR, elevated concentrations of acute phase proteins, leukocytosis, and sometimes anemia of chronic disease. ESR and C-reactive protein (CRP) concentrations are continuously increased throughout the course of disease, peaking during exacerbations. Complement factors are normal or increased. Decreased concentrations of complement could indicate either an alternative diagnosis or possibly a genetic complement factor 4a (C4a) deficiency, which has been reported in 2 patients (59). Leukocytosis was found in 69%, although lymphopenia was reported in 3 cases (4,62) (Nikolova, personal communication).



**Figure 2** Monoclonal IgM-kappa (A) and IgG-kappa (B) bands on serum protein electrophoresis with immunofixation. (Courtesy of G. van de Wiel, Department of Blood Transfusion and Transplantation Immunology, University Medical Centre St Radboud, Nijmegen.)

The evaluation of a patient with recurrent fever and urticaria should also include tests to exclude hematological, infectious, and autoimmune diseases (see “Differential Diagnosis”), eg, a complete blood count, blood cultures, serology for hepatitis C, and streptococcal antibodies, tests for rheumatoid factor, antinuclear antibodies, cold agglutinins, cryoglobulins, and ferritin.

Skin biopsies of urticarial lesions show heterogeneous histopathological findings, ranging from neutrophilic urticaria (most common) to spongiotic dermatitis (17). Vasculitis, predominantly described as leukocytoclastic, was found in 25% (22 of 87 patients).

On radiological examination of the skeleton, bone densification is the most frequent finding (48%). If present, it is often related to the sites of bone pain, but bone pain without obvious bone abnormalities occurs as well. Bone-marrow examination is normal in 80% of patients at the time of diagnosis. Nonspecific polyclonal lymphocytic or

plasmocytic infiltrates were found in the remaining cases. Biopsy of lymph nodes shows nonspecific inflammation.

In 1 patient, an ultrasound scan of the abdomen was performed because mild gamma-glutamyl-transferase elevation disclosed multiple hepatic lesions. The liver histology showed incipient nodular regenerative hyperplasia, as is often found in patients with autoimmune or hematological disorders (38). Although hepatomegaly was found in 29% of cases, hepatological findings were nonspecific in these cases.

## DIFFERENTIAL DIAGNOSIS

Before the diagnosis of Schnitzler syndrome can be made, a number of disorders have to be excluded (Table 5); we will discuss a few of them in more detail.

### Chronic Urticaria

The relevant differential diagnosis of the chronic urticaria includes chronic idiopathic urticaria (81). Schnitzler syndrome can be distinguished by the presence of the accompanying features, particularly the paraprotein, and the inefficacy of antihistamines. Recently, a useful guideline for classification and diagnosis of urticaria was published as a result of the Second International Consensus Meeting on Urticaria (82). In delayed-pressure urticaria, fever, arthralgias, and myalgia can accompany the urticaria in se-

**Table 5** Differential Diagnosis

Autoimmune disorders
Adult-onset Still's disease (AOSD)
Systemic lupus erythematosus (SLE)
Acquired C1 esterase deficiency
Hematological disorders
Monoclonal gammopathy of unknown significance (MGUS)
Polyneuropathy, organomegaly, endocrinopathy, monoclonal gammopathy, and skin changes (POEMS) syndrome
Waldenström's macroglobulinemia (WM)
Lymphoma
Multiple myeloma (MM)
Hereditary auto-inflammatory syndromes
Cryopyrin-associated syndrome (CAPS)
Familial cold urticaria (FCAS)
Muckle-Wells syndrome (MWS)
Chronic infantile neurologic cutaneous and articular syndrome (CINCA/NOMID)
Infectious diseases
Hepatitis B, C
Chronic meningococcemia
Other
Idiopathic chronic urticaria
Hypocomplementemic urticarial vasculitis
Delayed pressure urticaria
Cryoglobulinemia
Behçet's disease
Mastocytosis

vere cases. In contrast to Schnitzler syndrome, this is not associated with a paraprotein, elevated ESR, anemia, or leukocytosis (83).

An urticarial skin rash can sometimes also accompany systemic lupus erythematosus (SLE). Many of the systemic features of Schnitzler syndrome, such as fever, arthralgias, and anemia, are also seen in SLE. However, in SLE, the skin eruptions tend to be more persistent and to appear in a specific shape, such as the butterfly-shaped facial rash, and there is often specific organ involvement in SLE which is absent in Schnitzler syndrome. Antinuclear antibodies, which are common in SLE, can be detected in only 10% or fewer of Schnitzler syndrome cases. A monoclonal paraprotein is not found in SLE (41).

In acquired C1 esterase inhibitor deficiency (AC1ID), angioedema is much more common than in Schnitzler syndrome, and it is often associated with B-cell lymphoproliferative disorders. Low C4- and C1-inhibitor levels are typical. The skin eruptions and vasculitis that might appear in AC1ID differ from those in Schnitzler syndrome (83).

### Periodic Fevers

Adult-onset Still's disease (AOSD) resembles Schnitzler syndrome in being a disorder of unknown origin characterized by recurrent fever, rash, arthralgia, and/or myalgia. The diagnosis of AOSD can also only be made by exclusion; the only somewhat specific finding is an elevated serum concentration of ferritin. However, the rash in AOSD is more maculopapular or erythematous in appearance, rather than the urticarial lesions seen in Schnitzler syndrome. Bone pain with hyperostosis, and especially monoclonal gammopathy, is not found in AOSD (66).

The combination of urticaria and recurrent fever is also strikingly found in certain types of the cryopyrin-associated periodic syndrome (CAPS). This is a hereditary autoinflammatory syndrome with intermittent fever episodes, caused by mutations in cryopyrin, which can result in at least 3 recognized phenotypes, with some overlap among them. One of these phenotypes, also known as familial cold autoinflammatory syndrome, is characterized by an urticarial rash, which typically appears after exposure to cold. Another, known as Muckle-Wells syndrome, is often accompanied by amyloidosis and deafness. Features which may distinguish these 2 phenotypes of CAPS from Schnitzler syndrome include onset of symptoms at a younger age, a family history of the disease, and the absence of a paraprotein (84). The third clinical phenotype associated with cryopyrin mutations is chronic infantile neurologic cutaneous and articular syndrome (also known as neonatal-onset multisystemic inflammatory disorder); the severe complications of this syndrome, which include chronic sterile meningitis, progressive visual and severe auditory defects, and abnormal growth and neurologic development (85), distinguish it very clearly from Schnitzler syndrome.

Another hereditary autoinflammatory syndrome that is often mentioned in the differential diagnosis of Schnitzler syndrome is the hyper-IgD and periodic fever syndrome (HIDS). However, the clinical presentation of HIDS is very distinct from that of Schnitzler syndrome. In more than 90% of classic HIDS patients the recurrent fever episodes start in the first year of life, and all of them had their first symptoms before the age of 12 years. The rash, which can accompany the fever in HIDS, is not urticarial but rather erythematous, with petechiae and purpura. Between the febrile attacks, HIDS patients are generally symptom-free. A monoclonal paraprotein has never been detected in HIDS; the IgD elevation is always polyclonal (86).

### Paraproteins

Theoretically, monoclonal gammopathy of undetermined significance (MGUS), an isolated asymptomatic gammopathy, could exist in association with chronic urticaria of other causes, and thereby mimic the syndrome. However, the particular combination of symptoms in Schnitzler syndrome is quite specific. Also, MGUS and Schnitzler syndrome differ in the associated type of lymphoproliferative disorder; when a malignancy develops, in the case of MGUS, this is generally multiple myeloma, whereas in Schnitzler syndrome, it is typically WM (80).

Polyneuropathy, organomegaly, endocrinopathy, monoclonal gammopathy, and skin changes (POEMS) syndrome is a rare multisystemic disease of unknown origin that occurs in the setting of plasma cell dyscrasia. Circulating M-components of POEMS syndrome consist mainly of IgG or IgA-lambda, in contrast to the IgM of Schnitzler syndrome. Instead of urticaria, the most common dermatologic changes in POEMS include hyperpigmentation and plethora (87). Endocrinopathy is not associated with Schnitzler syndrome.

An IgM monoclonal gammopathy is also found in WM, a hematological malignancy further characterized by the infiltration of lymphoplasmacytic cells into bone marrow (88). As shown under "Prognosis," there is a remarkable relationship between Schnitzler syndrome and WM.

### TREATMENT

Table 6 shows the effects of the main therapies reported in the literature. For many years, no treatment option had proved satisfactory. Antihistamines are not effective in controlling the rash, and they are not indicated. The fact that antihistamines are ineffective, and that the urticarial rash in Schnitzler syndrome is nonpruritic in more than half of the cases, suggests a histamine-independent etiology of the rash.

Corticosteroids decrease symptoms significantly in 39% of patients. However, as almost invariably high-dose regimens are needed, their use is limited by the side effects. Colchicine is highly effective in some (4 of 19) patients (11,12,28,39), but ineffective in most cases.

Table 6 Therapeutic Options studied in SS

Treatment	Reported No of patients	Efficacy (no. of patients)		Overall High <sup>a</sup> efficacy (%)	References
		High <sup>a</sup>	Moderate <sup>b</sup>		
Corticosteroids	64	25	21	39	(1,3–8,10,12–15,17–24,26–28,30,31,34,35,39,41–50,52–67,70,91) (Akhras, Gül, Brinkman, Nikolova: p.c.)
Cox-inhibitors <sup>1</sup>	44	6	16	14	(1,5,6,8,11,12,17–19,21–24,28–30,33,35,37,39,40,42,44,45,48,49,52–57,59,60,64,65,67,69,70,91) (Akhras, Nikolova: p.c.)
Alkylating agents <sup>2</sup>	31	3	9	10	(1,4,6–10,13,15,20,30,35,41,43–45,47,48,53,56–58,67) (Akhras, Gül: p.c.)
Antihistamines	42	0	1	0	(1,3,7,8,11,14,15,19,24,26,27,30,33,35,40,42,44,49,53,54,56–58,60–62,67,70,91) (Akhras, Brinkman, Nikolova: p.c.)
Colchicine	19	4	4	21	(1,8,11,12,18,19,24,28,33,35,39,42,44,48,53,56,59) (Akhras: p.c.)
IFN $\alpha$ <sup>3</sup>	11	4	2	36	(1,10,30,34,35,45,60,62) (Akhras: p.c.)
IL-1ra <sup>4</sup>	8	8	0	100	(19,45) (Akhras, p.c.; personal observation)
Thalidomide	6	3	1	50	(19,70,71) (Akhras, Brinkman: p.c.)
Cyclosporine	10	2	1	20	(19,24,30,41,45,53,56) (Akhras, Brinkman, Gül: p.c.)
Azathioprine	9	0	0	0	(11,30,45,49,51,53,54,57) (Akhras: p.c.)
Plasmapheresis	9	0	3	0	(8,10,30,42,49,51,53,62) (Akhras: p.c.)
IV immunoglobulins	6	0	2	0	(30,39,45,49,56) (Akhras: p.c.)
Dapsone	12	0	1	0	(1,10–12,19,24,30,33,44,51,61) (Akhras: p.c.)
Pefloxacin	2	1	1	50	(25) (Clauvel: p.c.)
Psoralene	4	0	0	0	(1,39,42,62)
PUV-A <sup>5</sup>	8	5*	1	63*	(1,14,45,47,57) (Akhras: p.c.)
UVB phototherapy	2	1	0	50	(27) (Akhras: p.c.)
UVA phototherapy	1	0	0	0	(62)
Bisphosphonates	5	3**	0	60**	(41,45,50,55) (Akhras: p.c.)
Anti-TNF <sup>6</sup>	2	0	0	0	(45) (Akhras: p.c.)
Chloroquine	4	0	0	0	(8,33,54) (Akhras: p.c.)
Hydroxychloroquine	2	1	0	50	(42,55)
Doxepine	3	0	1	0	(30,53,62)
Dihydroergotamine	1	0	1	0	(11)
Rituximab	3	0	2	0	(42,45,71)
e.c. immunoadsorption <sup>7</sup>	1	1	0	100	(10)
Sulfasalazine	1	0	0	0	(42)

1. Cyclooxygenase inhibitors; 2. alkylating agents: cyclophosphamide, methotrexate; 3. interferon- $\alpha$ ; 4. IL-1ra: interleukin-1 receptor antagonist: anakinra; 5. psoralene UV-A; 6. anti-tumor necrosis factor: etanercept; 7. extracorporeal immunoadsorption.  
p.c., personal communication.  
<sup>a</sup>High efficacy: complete remission of urticaria, fever, and musculoskeletal symptoms.  
<sup>b</sup>Moderate efficacy: partial or temporary remission of symptoms.  
\*Reduced urticaria only.  
\*\*Reduced bone pain only.

In recent years a few promising therapeutic options have emerged, although the numbers of treated patients are still small. Initially, interferon- $\alpha$  (IFN- $\alpha$ ) seemed to be a promising option (62,89). In 1 patient, after several other therapies had failed to improve symptoms, IFN- $\alpha_{2b}$  caused a major regression in urticarial lesions and bone pain during an 18-month follow-up. Urticaria relapsed 3 times, 2 of which were induced by attempts to stop IFN- $\alpha$  therapy. In this patient, the therapy was well tolerated (62). Later, it proved ineffective in 5 of 11 patients, and only partly effective in another 2. Furthermore, in view of the potential side effects, it must be used with caution.

Thalidomide appeared to be very effective as it induced remission in 3 of 3 cases, although it had to be stopped in 2 because of polyneuropathy (19,70). Recently, however, 2 patients did not improve on thalidomide (Akhras and Brinkman, personal communication), and another improved only temporarily (71). In addition, the potential serious side effects of thalidomide make it a less preferable option. Pefloxacin may also be a promising option in inducing remission, although its use has only been reported in 2 patients (25) (Clauvel, personal communication).

Anakinra, which is a synthetic analog of the endogenous IL-1 receptor antagonist, caused complete remission

in 8 of 8 patients (19,45) (Akhras, personal communication; AS, personal communication; unpublished observations). Remission was induced within 24 hours in both classical and variant Schnitzler syndrome with 100 mg (sc) anakinra and could be sustained with daily injections. The longest follow-up is now 3 years, with persistent remission. Some patients only require on-demand administration after variable intervals. However, in 3 patients whose treatment was stopped temporarily, a flare-up of symptoms appeared within 1 day, but symptoms faded as soon as anakinra was restarted (19) (unpublished observation). A similar experience was observed in a patient who unintentionally missed 2 doses of anakinra, leading to dramatic worsening of symptoms within 48 hours with rigors, fever, and recurrence of the rash. However, as soon as the drug was restarted, symptoms subsided (Akhras, personal communication). The sole side effect of anakinra in Schnitzler syndrome reported to date is an erythematous painful lesion at the injection site. At present, anakinra appears to be the treatment of choice in patients with severe symptoms.

## PROGNOSIS

Overall, Schnitzler syndrome has a favorable prognosis in terms of mortality, with 91% survival after 15 years (Fig. 3). Since the average age of onset is 51 years, this does not seem to differ from the general population at this age (eg, 89% 15-year survival rate in the general Dutch population; Statistics Netherlands 2005, [www.cbs.nl](http://www.cbs.nl)).

Schnitzler syndrome does require long-term follow-up due to the potential development of lymphoproliferative disorders, in particular, WM. In the group of 94 patients, 11 patients developed WM (4,6,9,13,16,34,58,67,90,91) (Nikolova, personal communication). A survival analysis of the occurrence of WM is given in Figure 4. Ten years after the onset of symp-

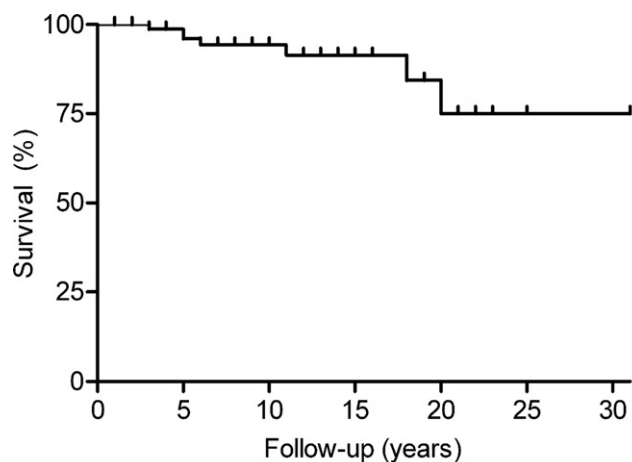


Figure 3 Survival in Schnitzler syndrome.

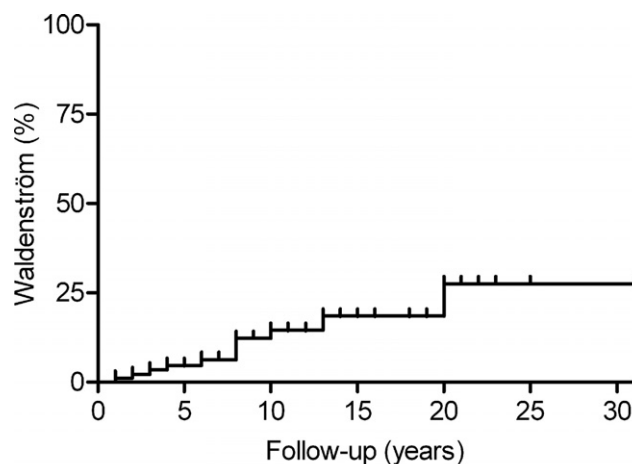


Figure 4 Incidence of Waldenström's macroglobulinemia in Schnitzler syndrome.

toms, WM occurred in 15% of cases. However, this might be an underestimation because of the limited number of patients at risk after a decade.

Development into other lymphoproliferative disorders has been identified in 3 cases: 1 had a lymphoplasmocytic lymphoma of which bone marrow involvement (required for the diagnosis of WM) is unclear (59), another patient developed myeloma (32), and recently, Dalle and coworkers reported the first known case of Schnitzler syndrome that developed a marginal zone B-cell lymphoma (71).

Overall, the risk of developing a lymphoproliferative disorder as found in this Schnitzler syndrome cohort was very similar to that found by Kyle and coworkers in a cohort of patients with IgM MGUS (18% in 10 years) (92).

An evidence-based follow-up scheme for the M-component in Schnitzler syndrome has not been reported yet, as it has been, for example, for MGUS by Kyle and Rajkumar (80). It is not known whether this can be applied equally to Schnitzler syndrome. Symptoms that should prompt further investigation for possible malignant evolution include easy bleeding of mucous membranes, dizziness, and blurred vision—all part of the so-called hyperviscosity syndrome (88). This occurs in WM at high IgM levels: a steady increase in the paraprotein levels should raise suspicion.

Interestingly, there are no reports of the development of amyloid L (AL)-type amyloidosis, even after decades of monoclonal gammopathy. However, 3 cases of type amyloid A (AA) amyloidosis have been reported (40,52) (Lozano Gutierrez, personal communication). In 1 of them, renal and cardiac involvement caused renal failure and cardiac complications (52); another patient died of progressive renal failure (Lozano Gutierrez, personal communication). Development of AA amyloidosis is associated with prolonged elevation of acute phase protein concentrations, specifically serum AA protein.

No spontaneous remissions have been reported, and most of the sparse treatment-induced remissions failed to last after dose reduction or stopping treatment (19,62). The long-term effects of the different therapies on symptoms, paraprotein level, and incidence of WM are still unclear.

## DISCUSSION

Analysis of follow-up data on 94 patients with Schnitzler syndrome in the present review reveals new information on the long-term prognosis and complications of this disorder. For this review, we adopted the definition of Schnitzler syndrome from Lipsker and coworkers (1). This raises a problem for Schnitzler syndrome-like cases which lack 1 of the 2 major criteria. For example, 1 patient presented with bone pain, bone densification, and a monoclonal IgM $\kappa$  gammopathy, in the absence of urticaria (93). There have also been reports of patients with a typical clinical phenotype resembling Schnitzler syndrome, but without the M-component (94,95). This last group of patients could well contain Schnitzler syndrome patients, as the monoclonal gammopathy may become detectable even several years after the onset of symptoms. Still, as the official definition stands, the diagnosis can only be made at the time both chronic urticaria and a monoclonal gammopathy are detected. Therefore, we did not include the aforementioned cases in our database.

Schnitzler syndrome does not seem to be an inherited disorder, but the fact that the father of the youngest case had MGUS leaves open the possibility of a genetic predisposition to other B-cell disorders.

In view of the potential development of WM or other lymphoproliferative disorders, it is interesting that Treon and coworkers recently reported that, of 257 patients with WM, 48 (19%) had at least 1 first-degree relative with either WM (5%) or another B-cell disorder including MGUS (2%). Patients with a family history of WM or a plasma cell disorder were diagnosed at a younger age and with greater bone marrow involvement (96).

Some observers feel that Schnitzler syndrome may be an indolent presentation of a slowly developing lymphoproliferative disorder which becomes clinically apparent after several years. In some early reports, Schnitzler syndrome was considered a paraneoplastic phenomenon (13). Indeed, 11 patients in the present data set developed WM in the long term, but clear evidence for this hypothesis is lacking, and we have shown that most patients survive for many years without developing a lymphoproliferative disorder.

Since WM is characterized by a monoclonal component of the IgM type, and all Schnitzler syndrome patients who developed WM had this type of paraprotein, the risk of malignant development in the IgG-type Schnitzler syndrome cases is unclear. To date, none of the 8 cases with the IgG variant have developed a lymphoproliferative disorder, at a maximum follow-up of 21 years (53).

Whereas the results of a wide range of treatments had been disappointing for a long time, recent developments seem promising. The striking effects of IL-1 inhibition may indicate a new era in which patients with Schnitzler syndrome do not have to suffer from this chronic disease. Anti-IL-1 therapy must be tried in more patients with long-term follow-up to establish its long-term effect on clinical symptoms and the development of WM or amyloidosis.

Schnitzler syndrome remains an enigmatic disorder that is hard to categorize. Is it primarily an immunological, hematological, or dermatological disease? Central to the clinical phenotype is a systemic inflammatory response to an unknown trigger. In this, it resembles the hereditary periodic fever syndromes, and most especially among these, the cryopyrin-associated periodic syndrome. In addition to a similarity in clinical phenotype, the impressive response to treatment with IL-1 blockers in several of these syndromes resembles that seen in Schnitzler syndrome (97-99).

These hereditary periodic fever syndromes have been relabeled “hereditary autoinflammatory syndromes” (100). This name aptly reflects the similarities to autoimmune disorders, while at the same time setting them apart. In the autoinflammatory syndromes it appears to be the innate immune system that is malfunctioning, while in the autoimmune disorders the fault lies primarily in the adaptive or acquired immune system.

We and others have previously suggested that Schnitzler syndrome should be regarded as an acquired autoinflammatory syndrome (19,45). It is our hypothesis that the main pathophysiological defect should be sought for in the innate immune system.

To increase our understanding of this rare syndrome, it is necessary to collect the experience of physicians around the world. We have made a start by collecting patient data in this present review. Another initiative is the website, [schnitzlersyndrome.com](http://schnitzlersyndrome.com), which offers a reference list of scientific literature on Schnitzler syndrome and aims to be a platform for clinical and/or research initiatives on the subject.

## ACKNOWLEDGMENTS

The following participants of the Schnitzler syndrome study group contributed to the present study.

We thank the following persons for data on not previously published patients and their permission to include them in this study: Akhras V, Department of Dermatology, St. George's Hospital, London, United Kingdom; Branten A, Department of Rheumatology, Radboud University Nijmegen Medical Centre, Nijmegen, The Netherlands; Brinkman K, Department of Internal Medicine, Onze Lieve Vrouwen Gasthuis, Den Haag, The Netherlands; Gül A, Department of Internal Medicine, Division of Rheumatology, Istanbul faculty of Medicine, Istanbul, Turkey; Lachmann HJ, Department of Medicine, Na-

tional Amyloidosis Centre, Royal Free and University College Medical School, London, United Kingdom; Nikolova K, Department of Dermatology and Venereology, Medical University, Sofia, Bulgaria.

We would like to acknowledge the help of the following physicians for supplying follow-up data on patients with Schnitzler syndrome from previous publications: Baleva M, Faculty of Medicine, Centre of Allergology, Laboratory of Clinical Immunology, Sofia, Bulgaria; Baty V, Clinique Mutualiste Eugene André, Lyon, France; Clauvel J-P, Department of Immunohematology, Hôpital Saint-Louis, Paris, France; De Saint-Pierre V, Department of Rheumatology, CHU Brest, France; Imrie KR, Toronto Sunnybrook Regional Cancer Centre, Toronto, Canada; de Kleijn EMHA, Department of Internal Medicine, Radboud University Nijmegen Medical Centre, Nijmegen, The Netherlands; Lipsker D, Department of Dermatology, Hôpitaux Universitaires, Strasbourg, France; Lorette G, Department of Dermatology, Hôpital Trousseau, Tours, France; Oborilova A, Department of Internal Medicine-Hemato-oncology, University Hospital Brno, Czech Republic; Peronato G, Department of Rheumatology, Ospedale S. Bortolo, Vicenza, Italy; Verret JL, Department of Dermatology, CHU, Angers, France; Worm M, Allergy-Center-Charite, Department of Dermatology and Allergy, Charite-Universitätsmedizin Berlin, Germany.

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